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Attorney Docket No. P66014US1
Appln. No. 09/879,814

REMARKS

Claims 49-59 are presented, hereby, in place of claims 38-48.

Present claim 49 corresponds to claim 38, amended by inserting "chromatographic" in line 3, before "separation." Adding this word to the claims effects expressly reciting what was, already, inherently recited, as further explained below.

Applicants wish to thank the examiner for expressly indicating in the Advisory Action that claims 38-48 overcame the rejection of record under 35 USC 112, second paragraph. However, Applicants question why claims 38-48 were not entered.

According to the Advisory Action, replacement claims 38-48 submitted in the Amendment "will not be entered because they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal." At the same time the Examiner acknowledges that the Amendment overcomes the rejections of record under 35 U.S.C. §112, second paragraph and, so, does in fact reduce the issues on appeal.

Claims 27-37 are rejected under 35 USC 103(a) for alleged obviousness, based on the combined teachings of US 5,585,007 (Antanavich) and US 4,733,446 (Holm). Reconsideration is requested in view of the instant amendment.

By the instant amendment rejected claim 27 is revised, as claim 49, such that, *inter alia*, the recited "separation medium" is changed to "chromatographic separation medium," i.e., the first step of the claimed process reads (claim 49, *emphasis added*):

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- blood plasma or said mixture is applied to a *chromatographic separation medium having an annular design* and having a layer of application medium of spherical particles with a hydrophobic surface applied thereon.

Thus, present claim 49 specifies what was *inherent* in claim 27; the instant invention provides a process involving "annular chromatography," i.e., as described at page 1 of the specification (*emphasis added*):

It has been found that high molecular weight substances can be separated and isolated within an order of magnitude by *annular chromatography*.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). A "ground of rejection is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002). When conducting an obviousness analysis, "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. 103 and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982).

Neither Antanavich nor Holm deals with chromatography; for example Antanavich tries to filter off cells from blood in order to obtain a concentrated blood plasma. The presently claimed invention, however, deals with the further purification of plasma or other blood plasma fractions for

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isolation of components dissolved in the plasma or the plasma fractions. Therefore, at best the Antanavich process provides a starting material for the process of the presently claimed invention.

Since all limitations on the present, and rejected, claims are not found in the cited references, the rejection under §103(a) cannot be maintained and, withdrawal after rejection is in order.

Additionally, applicants maintain that the rejection under §103(a) cannot be maintained as explained in their reply filed June 19, 2003, at pages 5-11. For the Examiner's convenience, the aforesaid explanation is repeated, below.

According to the statement of rejection, Antanavich fully meets the features (limitations) of the claims (Office Action page 3, 2nd, incomplete ¶, with one exception, i.e., the reference "does not explicitly teach separation of one protein from another per se" (Office Action, page 4, line 1).

With respect to Holm, the statement of rejection alleges that the reference fully meets the features of the present claims (Office Action page 4, lines 2-11), with the exception of using "spherical particles with a hydrophobic surface applied thereon as an application medium" (Office Action, page 4, lines 11-12).

According to the statement of rejection, one skilled in the art would have been motivated to combine the teachings of Antanavich and Holm because (allegedly):

Antanavich et al. teach the advantages of using spherical particles with a hydrophobic surface as an application medium for use in annular centrifugal separation device for the purpose of isolating blood plasma and [because] Holm teaches the advantage of isolating proteins from blood plasma using a similar annular, centrifuge separating medium.

(Office Action, page 3, lines 13-16). As allegedly motivated, the statement of rejection maintains that it would have been obvious for one skilled in the art to

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combine the features from each of the cited references in such a way that the resulting combination is the same as the presently claimed combination of features.

The rejection under §103(a) cannot be maintained because it relies on an incorrect interpretation of Antanavich. Allegations in the statement of rejection to the contrary notwithstanding, more than one feature of the rejected claims is missing from the cited reference, i.e., "separation of one protein from another per se" (Office Action, page 4, line 1) is not the only claim feature absent from Antanavich.

The statement of rejection evidences an apparent misinterpretation of Antanavich in connection with application of the reference teachings to a limitation on the rejected claims.

The subject matter of the rejected claims (claim 27 and claims dependent thereon) is patentably distinct from the state of the art by the use of an application medium of spherical particles with a hydrophobic surface applied thereon. The inventors found that such an application medium is highly advantageous when used for the separation of human plasma proteins in combination with a separation medium having an annular design.

The advantages of such a separation process of plasma proteins with hydrophobized particles was explained in detail in the Amendment filed January 2, 2003, and supported by the experimental protocol in the appendix submitted therewith. For the Examiner's convenience the remarks at issue set forth in the aforesaid Amendment (at pages 6-7) are reproduced below.

The inventors of the presently claimed invention realized that, surprisingly, for the purification of human plasma proteins, even from crude mixtures comprising various proteins, the use of an application medium of spherical particles with a hydrophobic surface is applicable and advantageous. The activity of the protein components remain basically unaltered, in contrast to what was observed by methods of the prior art. The state of the art clearly taught away from such a solution. The inventors actually did the

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opposite of what was taught, i.e., by using hydrophobic instead of hydrophilic surfaces.

In order to substantiate these findings, the inventors performed comparative examples, which are submitted herewith as Appendix. The comparative examples show how the activity of various important proteins from plasma pools is altered when they are incubated with glass beads according to the prior art (series C), and how the activity remains, essentially, unaltered, when they are incubated with hydrophobized glass beads, which are silicon oil treated (series B). A comparison with series A, wherein no beads are applied as a control, shows that the application medium of the invention has almost no effect on the activity of the plasma pool proteins. Therefore, they can be used as an application medium to prevent overflow and mixing of the eluents.

According to the statement of rejection, Antanavich discloses spherical particles having a hydrophobic-foam surface, citing in support the reference passage at column 13, lines 20-23. The cited passage concerns optional embodiments of the Antanavich invention, i.e.:

Optionally, the plasma may be contacted with dextranomer beads that have been bonded by electrostatic force with an open, hydrophobic cellular foam 15 (in accordance with the apparatus of FIGS. 1 and 3).

Reliance on the cited passage by the statement of rejection is misplaced as it takes the passage out of context and, by doing so, does not give a fair representation of the references teachings.

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

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In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986). It is the combined teachings of the prior art, taken as a whole, which must be considered in an obviousness analysis. *Ryko Manufacturing Co. v. Nu-Star, Inc.*, 21 USPQ2d 1053 (Fed. Cir. 1991).

A complete reading of Antanavich clearly shows that the optional embodiments relied on to meet the limitations of the rejected claims are patentably different from the subject matter of the rejected claims.

The passage cited in the statement of rejection merely indicates a superficial similarity between the optional embodiment of Antanavich and the presently claimed invention. Naturally, since the presently claimed process and the optional embodiment can only be performed with aqueous solutions, neither process can start before the beads are wetted.

Immediately following the cited passage, the text continues: "When wetted, the beads lose their electrostatic attraction and begin to swell" (Antanavich column 13, lines 23-24). This sentence, alone, clarifies that the optional embodiment partially described in the cited passage of Antanavich does not meet the claim features as alleged in the statement of rejection.

According to rejected claim 27, an aqueous mixture is applied to a separation medium having an annular design and having a layer of application medium of spherical particles with a hydrophobic surface applied thereon. The separation medium does not lose its integrity, i.e., fall apart into hydrophilic spherical particles and a hydrophobic surface layer, when used in the rest of the process steps, i.e., the steps, whereby, "said separation medium . . . is rotated," "an eluant is passed through the separation medium," and "fractions . . . exiting at the end of the separation medium . . . are collected."

In contrast to the presently claimed process, according to Antanavich, as soon as the aqueous probe is applied, the device comprises beads having a hydrophilic surface, which beads are distributed in an open, hydrophobic cellular foam. The material of the

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beads according to Antanavich has to be hydrophilic, i.e. the reference teaches (column 13, line 60, to column 14, line 7) :

In essence, any material *that absorbs water . . .* and which does not significantly denature the proteins essential to blood clotting . . . can be used as a concentrator . . . However, beads employed as described both above and hereunder are the preferred concentrator. [Emphasis added.]

The hydrophilic beads according to Antanavich may be selected such that they fractionate the plasma proteins (Antanavich column 14, lines 17 to 44). Here, again, Antanavich differs completely - and patentably - from the presently claimed invention; the presently claimed invention is based on a different principle.

A principle on which the presently claimed invention is based employs chromatography, which means a method for separation of dissolved molecules in a liquid sample. On the other hand, Antanavich teaches the separation of solid particles, such as blood cells, from a liquid, such as plasma. The presently claimed invention uses molecular interaction between a stationary and a mobile phase; whereas, the method of Antanavich uses mechanical means, namely, gravitational force.

The function of the hydrophobic, open-cell foam is to trap red and white blood cells (Antanavich column 13, lines 11 to 13).

The embodiments illustrated in Antanavich FIGS. 1 and 3 are explained in detail in the reference's passage at column 19, lines 3-46. In the passage at column 17, lines 13-18, Antanavich discloses that the porosity of the foam is selected such that the foam either retains cells, or retains the concentrator beads. This shows, clearly, that the hydrophobic foam does not function in any way in the separation of plasma proteins, in contrast to the presently claimed invention.

Accordingly, Antanavich does not teach or suggest the separation of plasma proteins from a mixture, which mixture is applied to a separation medium having an annular

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design and having a layer of application medium of spherical particles with a hydrophobic surface applied thereon.

The statement of rejection admits that Holm "does not teach the use spherical particles with a hydrophobic surface applied thereon as an application medium" (Office Action page 4, lines 11/12). Accordingly, Holm provides nothing to cure the fatal deficiencies in Antanavich as explained above.

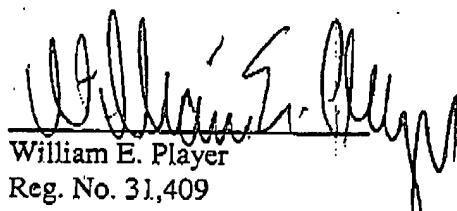
As such, the references cited in the ground of rejection under §103(a) fail to support each limitation of the rejected claims. Accordingly, the "ground of rejection is simply inadequate on its face, *Thrift*, 63 USPQ2d at 2008, and withdrawal of the rejection is in order.

Favorable action is requested.

Respectfully submitted,

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